Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients

SUPPLEMENTAL INFORMATION

Study Objectives

Primary Objective

The primary objective of this trial was to evaluate the efficacy of roxadustat in the correction of anemia in NID subjects.

Secondary Objectives

The secondary objectives of this trial were as follows:

- Evaluate the safety of roxadustat in the correction of anemia in NID subjects.
- Evaluate the effect of iron supplementation when used concomitantly with roxadustat in the correction of anemia in NID subjects.
- Evaluate a combination of initial roxadustat doses and dose level adjustments to optimize anemia management in NID subjects.
- Compare roxadustat doses and Hb responses between HD and peritoneal dialysis (PD) subjects.
- Evaluate quality of life measures using Short Form 36 (SF-36) and Functional Assessment of Cancer Therapy (FACT-An) questionnaires.

Exploratory Objectives

The exploratory objectives of this trial were as follows:

- Assess iron utilization parameters during anemia therapy with roxadustat.
- The effect of roxadustat on exploratory biomarkers may also be analyzed.

Overall Study Design Plan Description

This was a randomized, open-label, dose-titration study in NID subjects not receiving ESA treatment.

Subjects on HD were randomized to one of three arms (A, B, or C, with ~12 subjects in each arm) in a 1:1:1 ratio, to receive either no iron supplementation, PO iron supplementation, or IV iron supplementation, in addition to roxadustat. Subjects on PD were enrolled into Arm D (and received PO iron supplementation in addition to roxadustat).

Arm E was an optional, confirmatory/supplemental arm with flexible dosing and flexible iron supplementation based on the evaluation of data from the previous 4 arms. Based on the

results of Arms A through C, HD subjects were enrolled in Arm E and received roxadustat without iron supplementation.

Following the Screening Period (up to 4 weeks), eligible subjects entered a 12-week Treatment Period during which they were to attend weekly study visits. After the Treatment Period, subjects were followed in a 4-week Post-Treatment Follow-Up Period.

The baseline Hb value for efficacy analysis was defined as the mean of three central laboratory Hb values: the last two screening Hb values prior to randomization plus the one Hb value on Day 1 of the Treatment Period, prior to receiving the first dose of the study drug.

Safety was assessed by medical history, vital signs, physical examinations, clinical laboratory values (including liver function tests [LFTs] and complete blood counts), electrocardiograms (ECGs), adverse events (AEs) and concomitant medication reporting.

This study was designed to assess the optimal safe and effective initial doses of roxadustat and the dose adjustment regimen required to correct anemia and maintain Hb to achieve a desired Hb range in NID subjects over a treatment period of 12 weeks. Incident dialysis patients generally require large doses of ESA and IV iron to achieve Hb correction, secondary to uremic inflammation and variable degrees of iron depletion. Thus, this study provided an opportunity to fully compare the effectiveness of roxadustat in correcting anemia without any iron supplementation, with PO iron and IV iron supplementation.

Roxadustat doses between 1.0 and 1.7 mg/kg TIW were selected as the starting doses (in mg, adjusted for body weight) in Arms A through C of this study in a simplified tiered, weight-based approach: 60 mg in 40 to 60 kg subjects, 100 mg in >60 to 90 kg subjects, and 140 mg in >90 to 140 kg subjects. A transition was made from mg/kg dosing (FGCL-SM4592-017 and FGCL-4592-040 prior to Amendment 3) to tiered, weight-based dosing (FGCL-SM4592-041 and FGCL 4592-040 after Amendment 3) in all study arms (Arms A through E) to optimize dosing convenience of a solid oral dosage form of roxadustat while taking into account the subject's body weight to minimize over- or under-dosing. Hemoglobin responses to roxadustat enabled assessment of the impact of no iron supplementation when compared with PO iron, and IV iron supplementation.

Dosing duration was 12 weeks, with the primary emphasis being placed on evaluating Hb correction followed by maintenance. Arm E was an optional, confirmatory or supplemental treatment arm to either confirm and/or refine the dosing regimens initially evaluated in Arms A through D and/or evaluate the effects of iron supplementation on erythropoiesis while subjects were treated with roxadustat.

Roxadustat doing was fixed during the Treatment Period, except during Weeks 5 and 9 when dose adjustment rules were implemented. These dose adjustment rules allowed a patient's dose to be titrated in order to increase and maintain Hb values to above 11 g/dL, without an intentional increase above 13.0 g/dL. The maximum roxadustat dose was 2.5 mg/kg.

Additionally, this study assessed whether or not supplemental (IV or PO) iron was necessary for erythropoiesis using roxadustat. Subjects in Arms A and E received no iron supplementation, subjects in Arm B received only PO iron supplementation and subjects in Arm C receive IV iron.

Selection of Study Population

Inclusion Criteria

Subjects must have fulfilled all of the following eligibility criteria for participation in the study:

1. Age 18 to 80 years
2. Receiving HD or PD for native kidney ESRD for a minimum of 2 weeks and a maximum of 4 months, prior to randomization
3. Ferritin between 50 and 300 ng/mL
4. Transferrin saturation (TSAT) between 10 and 30%
5. Mean of the two most recent Hb values during the Screening Period, obtained at least 7 days apart, must have been ≤ 10.0 g/dL, with a difference of ≤ 1.0 g/dL between the two values
6. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must have been ≤ 1.5 x the upper limit of normal (ULN) at screening
7. Total bilirubin (TBili) must have been ≤ the ULN at screening
8. Alkaline phosphatase (ALP) must have been < 2 x the ULN
9. Platelet count ≤ the ULN
10. Screening serum folate and vitamin B_{12} level ≥ lower limit of normal
11. Body weight 40 to 140 kg

Exclusion Criteria

Subjects who met any of the following exclusion criteria were not eligible for participation in this study:

1. Prior receipt of an ESA
2. Received IV iron within 4 weeks of randomization
3. Any clinically significant *inflammation*
4. or evidence of an underlying infection, as manifested by a total white blood cell (WBC) count > ULN, within 4 weeks prior to randomization
5. Positive for any of the following: human immunodeficiency virus (HIV), hepatitis B surface antigen (HB sAg), or anti-hepatitis C virus antibody (anti-HCV Ab)
6. History of chronic liver disease, including hepatitis A, B, C, or E, and alcoholic liver disease
7. Serum albumin <3 g/dL
8. New York Heart Association Class III or IV congestive heart failure
9. Myocardial infarction or acute coronary syndrome within 12 weeks prior to randomization

10. Thromboembolic event within 12 weeks prior to randomization, or taking an anticoagulant for a venous thromboembolic event (eg, deep vein thrombosis or pulmonary embolism)
11. Inadequately controlled hypertension (pre- and post-dialysis systolic BP [SBP] >170 mm Hg or diastolic BP [DBP] >110 mmHg) within 4 weeks prior to randomization. For any isolated BP value(s) above the 170/110 mmHg thresholds, the study medical monitor had discretion to allow study entry on a selected basis.
12. Diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma on renal ultrasound within 3 months prior to randomization
13. History of malignancy, except the following: cancers determined to be cured or in remission for ≥5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps
14. Chronic inflammatory disease that could have impacted erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it was in remission
15. Active or chronic gastrointestinal bleeding, or a known coagulation disorder
16. Hemoglobinopathy (eg, homozygous sickle-cell disease, thalassemia of all types, etc.)
17. History of myelodysplastic syndrome, multiple myeloma, or pure red cell aplasia
18. History of hemosiderosis, hemochromatosis or polycystic kidney disease
19. Active hemolysis or diagnosis of hemolytic syndrome
20. Known bone marrow fibrosis
21. Uncontrolled or symptomatic secondary hyperparathyroidism
22. Seizure disorder or receiving anti-epilepsy medication for seizure disorder within 12 weeks prior to randomization
23. Known proliferative retinopathy
24. Any prior or scheduled organ transplantation; a prior transplant that had been explanted was acceptable
25. Anticipated elective surgery that was expected to lead to significant blood loss during the study period
26. Life expectancy < 12 months
27. Drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that could have reduced absorption of study drug
28. Anticipated use of dapsone or acetaminophen > 2.0 g/day, or >500 mg per dose repeated every 6 hours, during the Treatment or Follow-Up Periods of the study
29. Androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to randomization
30. Use of herbal medicine within 4 weeks of randomization
31. RBC transfusion within 8 weeks prior to randomization or anticipated need for transfusion during the treatment period
32. History of alcohol or drug abuse within a year prior to randomization, or anticipated inability to avoid consumption of more than three alcoholic beverages per day

33. History of allergy or sensitivity to PO or IV iron therapy
34. Prior treatment with roxadustat or any experimental hypoxia-inducible factor prolyl-hydroxylase inhibitor
35. Use of an investigational medication or treatment, participation in an investigational interventional study, or carryover effect of an investigational treatment expected, within 4 weeks prior to randomization
36. Pregnant or breastfeeding females
37. Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who were not on birth control unless the male subject agreed to use contraception
38. Any medical condition that in the opinion of the investigator may have posed a safety risk to a subject in this study or may have interfered with study participation

Removal of Patients from Therapy or Assessment

Subjects could withdraw from the study at any time. In the event of withdrawal, subjects were strongly advised to complete the 4-week Follow-up Period. Subjects were to be discontinued from the study for any of the following reasons:

- Significant noncompliance with study procedures, as determined by the principal investigator and study medical monitor
- Subject no longer consented to participate in the study
- Physician decision that it was in the best interest of the subject to be withdrawn from the study
- If the study medical monitor and principal investigator agreed that a subject's intercurrent illness was significantly interfering with study assessments
- The study was terminated by FibroGen for any reason
- Subject was lost to follow-up for the duration of the study
- FibroGen's discretion
- Subject was found to be pregnant
- Death

Subjects who withdrew from the study were to be followed for AEs. The reason for withdrawal was recorded on the appropriate case report form (CRF).

Women of childbearing potential who withdrew from this study were to continue contraception for at least 12 weeks following the last roxadustat administration. Male subjects with partners of childbearing potential must have agreed to use a medically acceptable method of contraception during the trial and for at least 12 weeks following the last roxadustat administration.

Treatments

Roxadustat

Initial Dose

All subjects received roxadustat, administered three-times weekly (TIW). Subjects were assigned an initial roxadustat dose based on a tiered, weight-based, dosing scheme (**Error! Reference source not found.**). As an example, an 80 kg subject would have been categorized as having medium weight and would therefore have received an initial roxadustat dose of 100 mg TIW. The roxadustat dose was not to exceed 2.5 mg/kg per dose throughout the course of the study.

Initial Roxadustat Dose

Low Weight (40 to 60 kg)	**Medium Weight** (>60 to 90 kg)	**Heavy Weight** (>90 to 140 kg)
60 mg	100 mg	140 mg

Abbreviations: HD = hemodialysis.

NOTES: The weight of HD subjects was the post-dialysis dry weight at screening.

Dose Adjustments

Roxadustat doses were fixed during the Treatment Period, except during Weeks 5 and 9, when dose adjustments were implemented as follows:

- If Hb was <11.0 g/dL and the rate of rise of Hb was <1.0 g/dL in the previous 4 weeks, the roxadustat dose was escalated up one dose level (Table 2).
- The maximum roxadustat dose for any individual subject did not exceed 2.5 mg/kg per dose. For example, if a 100 kg subject required dose escalation to Dose Level 3, the subject was administered a roxadustat dose of 250 mg TIW (instead of 300 mg TIW).
- If Hb was >13.0 g/dL, or rate of rise of Hb was ≥2.0 g/dL in the previous 4 weeks, the roxadustat dose was reduced by one dose level, or by ~30% if the subject was at Dose Level 1.

Roxadustat Dose Levels for Dose Adjustment

Roxadustat Dose Levels	**Low Weight** (40 to 60 kg)	**Medium Weight** (>60 to 90 kg)	**Heavy Weight** (>90 to 140 kg)
1 (initial dose)	60 mg	100 mg	140 mg
2	100 mg	140 mg	200 mg
3	140 mg	200 mg	300 mg

Abbreviations: TIW = three times a week.

NOTES: A subject's roxadustat dose was not to exceed 2.5 mg/kg TIW.

Supplemental Iron Formulations

Oral iron (ferrous fumarate or ferrous gluconate) was supplied to subjects in Arms B and D. Throughout the Treatment Period, these subjects received a PO iron supplement at doses containing elemental iron between 50 and 195 mg daily, depending on the type of iron formulation available in their countries.

Intravenous iron (ferric gluconate complex in sucrose injection [eg, Ferrlecit®] or equivalent) was supplied for subjects in Arm C. These subjects received IV iron at a dose of approximately 60 mg (eg, 5 mL Ferrlecit, which contained 62.5 mg of elemental iron) every week. The IV iron supplement was withheld if ferritin was >800 ng/mL or TSAT >60%.

Identity of Investigational Product

Roxadustat was supplied by FibroGen, Inc. in white opaque hydroxypropyl methylcellulose (HPMC) capsules at strengths of 20, 50, or 100 mg.

Method of Assigning Subjects to Treatment Groups

The first 36 HD subjects were randomized centrally, stratified by baseline iron repletion status (TSAT ≥20% and ferritin ≥100 ng/mL versus TSAT <20% or ferritin <100 ng/mL), to three arms (A, B, and C) of ~12 subjects each in a 1:1:1 ratio to receive no iron supplementation, PO iron supplementation, or IV iron supplementation, respectively, in addition to roxadustat.

No randomization was performed for Arms D and E.

Selection of Doses in the Study

The starting roxadustat doses for this study were based on the nonclinical toxicology data, and data from Phase 1 and Phase 2a (FGCL-SM4592-017) human trials using roxadustat.

Nonclinical toxicology data showed that the no-observed effect level and the no-observed adverse effect level in monkeys were 10 and 30 mg/kg/day, respectively.

The first-in-human studies in healthy volunteers showed that single PO roxadustat doses of 0.3, 1.0, 2.0, and 4.0 mg/kg, and multiple PO roxadustat doses from 1.5 mg/kg to 3.75 mg/kg administered once weekly (QW), twice-a-week (BIW), or TIW for 4 weeks were considered safe and generally well tolerated. Dose-dependent increases in EPO and transient increases in reticulocyte counts were demonstrated, and Hb responses were observed.

Roxadustat doses were fixed during the Treatment Period, except during Weeks 5 and 9 when dose adjustment rules were implemented. These dose adjustment rules allowed dose titration in order to increase and maintain the subject's Hb values above 11 g/dL, without an intentional increase above 13.0 g/dL. The maximum roxadustat dose in this trial was 2.5 mg/kg.

Selection and Timing of Dose for Each Subject

Previous human experience with roxadustat in healthy subjects and subjects with CKD suggested that a TIW dosing regimen of roxadustat was more likely to provide therapeutic benefit in correcting anemia in subjects with CKD on dialysis than a less frequent dosing regimen.

Results from a nonclinical mass-balance study with radiolabeled roxadustat in rats demonstrated that approximately 80% of a dose was recovered in the feces and 20% in the urine, suggesting that renal excretion is a minor elimination pathway for roxadustat and that major dose accumulation is not expected in patients with renal insufficiency. In addition, the human pharmacokinetic (PK) profile of roxadustat suggests that a dosing interval of 48 or 72 hours during the week and 72 or 96 hours over the weekend was unlikely to lead to significant drug accumulation (<10%) with repeated, intermittent dosing.

At the time the protocol for this trial was developed, preliminary data from a Phase 2a study (FGCL-SM4592-017) in anemic CKD patients using roxadustat doses ranging from 0.7 to 2.0 mg/kg BIW or TIW (with doses ranging from 40 to 340 mg) suggested that roxadustat was well tolerated and demonstrated robust Hb responses to 4-week dosing in a dose responsive manner. Starting doses around 1.0 mg/kg administered TIW resulted in optimal mean rates of rise of Hb of approximately 1.0 g/dL over 4 weeks. There were no reports of hypertension, cardiovascular events, or thrombosis during study drug treatment in patients treated with 1.0 to 2.0 mg/kg BIW or TIW, while mean Hb increases were between 1.0 to 2.2 g/dL and responder rates were 50% to 100%, in a dose responsive manner. Furthermore, Study FGCL-4592-040, a conversion study in HD patients demonstrated that roxadustat doses of 1.0 to 2.0 mg/kg were well tolerated and appeared effective in maintaining Hb levels in the absence of IV iron supplementation over a 6-week treatment period.

A transition was made from mg/kg dosing (FGCL-SM4592-017) to tiered, weight-based dosing in Arms A through E to optimize dosing convenience of a solid PO dosage form of roxadustat while taking into account the patient's body weight to minimize over- or under-dosing. Hemoglobin (Hb) responses to roxadustat enabled assessment of the impact of no iron supplementation when compared to PO iron versus IV iron supplementation, to fully explore the therapeutic potential of roxadustat.

The dosing duration was 12 weeks, with the primary emphasis being placed on the evaluation of Hb correction followed by the maintenance of Hb levels. Arm E was an optional arm to either confirm and/or refine the dosing regimens initially evaluated in Arms A through D and/or to evaluate the effects of iron supplementation on erythropoiesis while subjects were being treated with roxadustat.

Blinding

This was an open-label study.

Prior and Concomitant Therapy

Allowed Concomitant Therapy

Concomitant medications included any prescription or over-the-counter preparations (including herbal products and "natural remedies") used by a subject while participating in this clinical trial. Changes to anti-hypertensive medications were kept to a minimum during the course of the study to enable a better assessment of the effect of study drug on BP.

For all concomitant medication use, the study site was asked to provide an indication for its use. If the stated indication was a nonspecific condition (eg, "rash"), documentation of the condition, as specific as possible, was requested from the subject's primary care physician and maintained in the subject's clinical study records as source documentation.

Prohibited Medications, Procedures, and Nondrug Therapies

Subjects were not permitted to consume more than three alcohol-containing drinks per day during the Treatment or Follow-up Periods.

The following concomitant therapies were prohibited:

- Androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to randomization, and until completion of the study.
- RBC transfusion within 8 weeks prior to randomization, and until completion of the study. These restrictions did not apply to subjects who were acutely hemorrhaging.
- Intravenous or oral iron supplementation for subjects in Arm A, or IV iron supplementation for subjects in Arms B or D. Iron supplementation was also prohibited in subjects in Arm E, after it was designated a no-iron arm. An exception was made for the use of rescue iron supplementation.
- Any ESA therapy until completion of the study (except for rescue).
- Dapsone or acetaminophen >2.0 g/day or >500 mg per dose repeated every 6 hours, from the day of randomization until completion of the study,
- Use of herbal medicine was strongly discouraged during the course of the study. If a subject insisted on starting use of a herbal medicine during the study, this should have been discussed and approved with the study medical monitor on a case-by-case basis.

Rescue Therapy

If a subject was not responding adequately to study medication (as described below), rescue therapy such as IV iron (in an arm that was not receiving IV iron supplementation), RBC transfusion, or use of an ESA, was allowed if considered clinically warranted by the subject's treating physician. Such cases, and subsequent study drug dosing, were discussed with the study medical monitor on a case-by-case basis. Inadequate response to study medication was defined as follows:

- Symptomatic from his/her anemia
- Hb level 1.0 g/dL or more below baseline Hb if baseline Hb <9.5 g/dL
- Hb level <8.5 g/dL if baseline Hb ≥9.5 g/dL

Rescue IV iron supplementation consisted of a dose of approximately 200, 250, or 300 mg IV iron for a 60, 70, or 80 kg subject, respectively.

Additionally, a subject who developed reactive thrombocytosis (platelet count >450 x 10^9/L or >150% of the baseline value) when ferritin was <30 ng/mL and TSAT <5% received IV iron supplementation unless otherwise noted.

Excessive Hematopoiesis

Excessive hematopoiesis was defined as Hb > 13.0 g/dL, or rate of rise of Hb ≥ 2.0 g/dL in the previous 4 weeks. If a subject had excessively high Hb values outside Weeks 5 and 9 (when roxadustat dose adjustments were allowed) that were of clinical concern, the investigator was allowed to immediately adjust the subject's roxadustat dose. The investigator could also perform a therapeutic phlebotomy.

Contraception

Female subjects of childbearing potential had to agree to use a medically-acceptable form of birth control (such as, but not limited to PO contraceptive pills, depo progesterone, or an intrauterine device). Abstinence alone sufficed as adequate contraception. Male subjects with sexual partners of childbearing potential who were not using birth control (as described above) were required to use contraception (eg, condom) if not surgically sterile (ie, vasectomy). Contraceptive methods were required from the time informed consent was signed and through at least 1 month after the last dose of study drug.

Treatment Compliance

All roxadustat doses were dispensed during each study visit and administered TIW. The subject was administered one dose of roxadustat at the study clinic. The remaining two doses for the week were dispensed into two separate take-home bottles. The subject was provided the two take-home bottles for self-administration at home. Each take-home bottle was returned by the subject at the next visit. In order to determine treatment compliance the date capsules were dispensed, the bottle number they were dispensed from, the total number of capsules in each bottle, the subject and site number, the total capsules dispensed, the total capsules in inventory, and any site comments were recorded by the Investigator or their designee.

Efficacy and Safety Variables

Primary Efficacy Variable

The primary efficacy variable was the maximum change in Hb from BL during Weeks 3 to 13.

Secondary Efficacy Variables

- Mean change in Hb from baseline during Weeks 5 to 8, 9 to 12, and 13 to 16
- Number (%) of subjects whose maximum Hb achieved within the 12 weeks of treatment is at least 1.0 g/dL increase from baseline and is ≥ 11.0 g/dL
- Number (%) of subjects with a Hb response, defined as an increase in Hb by ≥ 1.0 g/dL from baseline, by Week 5, 9, 13 and 16

- Number (%) of subjects achieving Hb 11.0 to 13.0 g/dL at Weeks 5 to 13
- Median time to Hb response (increase in Hb by ≥ 1.0 g/dL from baseline)
- Number (%) of subjects achieving Hb response to Dose Level 1, Dose Level 2, and Dose Level 3.
- Number (%) subjects requiring dose increase at Week 5 and 9
- Number (%) subjects requiring dose reduction or dose discontinuation due to excessive erythropoiesis
- Mean change in ferritin, transferrin saturation (TSAT), and reticulocyte Hb content (CHr) from baseline
- Number (%) of scheduled weekly Hb values within Hb 11.0 to 13.0 g/dL at Weeks 5 to 8, 9 to 12, and 13 to 16
- Number (%) of scheduled weekly Hb values within Hb 11.0 to 13.0 g/dL after reaching Hb ≥ 11.0 g/dL
- Number (%) of scheduled weekly Hb values below 11.0 g/dL after reaching Hb ≥ 11.0 g/dL.
- Number (%) of scheduled weekly Hb values in excess of 13.0 and 14.0 g/dL at Weeks 5 to 8, 9 to 12, and 13 to 16
- Number (%) of scheduled weekly Hb values ≤ 10.0 g/dL at Weeks 5 to 8, 9 to 12, and 13 to 16
- Number (%) of subjects requiring rescue treatment with an ESA, red blood cell (RBC) transfusion, or IV iron (excluding Arm C)
- Number (%) of subjects requiring therapeutic phlebotomy.
- Number (%) of subjects withdrawn from the study due to inadequate efficacy.
- Change in overall SF-36 score, physical functioning subscore, and vitality subscore at Weeks 9 and 13 from baseline.
- Change in overall FACT-An scores at Weeks 9 and 13 from baseline.

Clinical Laboratory Tests Assessed

All laboratory tests of blood specimens were performed by a central laboratory or FibroGen, except for human chorionic gonadotropin (hCG) pregnancy test in women of child bearing potential. This hCG test was performed at the study site's local laboratory. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory was provided to all participating sites.

Serum chemistry (including LFTs), iron studies (including transferrin, TSAT, ferritin, iron, sTfR), vitamin B_{12}, folate, and CBC with white cell differential and reticulocyte counts, were performed and analyzed by a central laboratory at screening, and during the Treatment and Post-Treatment Follow-Up periods.

The central laboratory also performed unscheduled testing (eg, to confirm abnormal LFTs or to obtain an additional Hb value). However, in no case was prudent or necessary testing delayed if it was not possible to send a sample to the central laboratory or if the turnaround time from the

central laboratory was not sufficiently rapid for clinical management of the subject. In such emergency/urgent situations, local laboratory test results were used to make clinical judgments that affect the safety of the study subject.

Required scheduled laboratory tests were to be performed by a central laboratory unless specified otherwise. Laboratory tests included the following:

- Serum Chemistry: sodium, potassium, chloride, calcium, magnesium, bicarbonate, phosphorus, blood urea nitrogen, creatinine, glucose, uric acid, albumin, total protein, lactate dehydrogenase, ALT, AST, bilirubin (total and direct), gamma-glutamyl transferase (GGT), ALP
- Complete Blood Count: Hb, Hct, RBC, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, WBC, neutrophils, banded neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count, reticulocyte count
- Coagulation Parameters: prothrombin time (PT) and calculation of an international normalized ratio (INR) in subjects whose LFT results triggered hepatic safety monitoring through the hepatic monitoring plan (HMP) were sometimes requested of the central laboratories
- ELISA for HIV
- HB sAG and Anti-HCV Antibody Test
- Serum Iron Studies: iron, ferritin, transferrin (or TIBC), and TSAT
- Additional Laboratory Analytes: vitamin B_{12}, folate
- Exploratory Biomarkers: Serum samples were collected and stored for future analysis of relevant exploratory biomarkers.

Additional Safety Assessments

Electrocardiogram

Twelve-lead ECGs, with single 10-second strips, were obtained from all subjects for safety assessments.

Renal Ultrasound

A renal ultrasound examination was required within 3 months prior to randomization to exclude the presence or suspicion of renal cell carcinoma.

Quality of Life Questionnaire

All study subjects were asked to complete Quality of Life questionnaires (SF-36 and FACT-An) at Day 1 (Week 1), Week 9, and at Week 13.

Additional Safety Monitoring

Subjects were closely monitored for inadequate or excessive hematopoiesis and managed according to guidelines stipulated in the protocol based on protocol-defined dose adjustment rules and reasons for study drug discontinuation. Liver function was also closely monitored and

investigators followed a HMP to determine when heightened surveillance was required and what actions, if any, were needed with study drug administration.

Hepatic Monitoring Plan (HMP)

The study protocol required approximately weekly screening of liver function tests (LFTs) during the treatment period and once every 2 weeks during the posttreatment extension visit period (changed from 4 weeks after study drug discontinuation to 12 weeks). If LFT results became abnormal at any time point, additional monitoring (i.e., the HMP) was to be performed. The HMP was intended to enable early detection and action following abnormal LFT results, and was implemented after a patient died from fulminant hepatitis in a clinical trial evaluating another experimental compound (FG-2216, also a HIF-PH inhibitor but structurally distinct from roxadustat). Investigator actions with respect to the HMP were summarized in an appendix to the study protocol. The study sponsor (FibroGen) trained site personnel on the HMP, and regularly monitored and summarized all LFT results and other safety data for the DMC. The DMC was specifically tasked with reviewing the LFTs and other safety data and making recommendations on study conduct and procedures and continuation or termination of the trial as necessary.

Statistical and Analytical Plans

Summary statistics consisted of the number of subjects (N), means, standard deviations, medians, and minimum and maximum values for continuous variables, and counts and percentages for categorical variables. For efficacy endpoints, the standard error and 95% confidence intervals were added as part of the descriptive summaries. Tables summarized all efficacy and safety measures by treatment group and time point, if appropriate. Summary tables indicated the number of subjects with complete data for each measurement, event or outcome. All analyses were based on available data unless otherwise specified.

Efficacy Analyses

Hemoglobin results obtained from the central laboratory were used for all efficacy analyses. Baseline Hb was defined as the mean of the last three central laboratory Hb values prior to the first dose of study treatment; baseline eGFR, ferritin, and TSAT levels were defined as the mean of the last two central laboratory values prior to the first dose of study treatment.

The primary efficacy analysis was based on the EE population, defined as all subjects who received at least two weeks of study treatment with valid corresponding Hb values. The EE population was primarily used in the efficacy analyses. The primary efficacy analysis was assessed using within-group maximum Hb change from baseline during Weeks 3 to 13 for each treatment arm and was analyzed using an analysis of covariance (ANCOVA) model.

The same analysis was repeated using the FAS population, defined as all subjects who were randomized, received at least one dose of study drug, and had at least one post-dose assessment. In addition, treatment effect between treatment arms were compared using an ANCOVA model with baseline Hb and stratification factors as covariates for continuous endpoints. Logistic regression was used to compare treatment effect between arms for

categorical endpoints with baseline Hb and stratification factors as the covariates. Number (%) of Hb responders and mean Hb change from baseline was summarized descriptively for Arms A through E at each scheduled time point. The dose level at the time of Hb response was summarized descriptively by treatment arm and for the overall population. The frequency of dose increases and decreases, and use of rescue therapy was tabulated through Weeks 5, 9, 13, and 16 for each treatment arm as well as for the pooled study population.

Median time to Hb response was estimated for each treatment arm using the Kaplan-Meier method. Hemoglobin response was defined as a Hb increase from baseline of at least 1.0 g/dL. In addition, median initial responsive time and dose was tabulated to evaluate when an initial Hb change from baseline reached at least 1.0 g/dL.

The number (%) of subjects, scheduled Hb values, and consecutive Hb values achieved for a variety of Hb ranges between 11.0 and 13.0 g/dL, as well as above or below these ranges, during 4-weekly study durations throughout the treatment period was tabulated.

Efficacy variables such as mean Hb values at Week 5, 9, 13, and 16 were compared to baseline values for all treatment arms.

Exploratory Analyses

Quality of life composite scores as well as selected subscale scores at Weeks 9 and 13 were compared to baseline values and between treatment arms. Descriptive statistics were generated for exploratory endpoints and biomarkers. Correlations between parameters were explored. Stratified and subgroup analyses of primary and secondary endpoints by baseline iron utilization parameters and other biomarkers were sometimes performed.

Safety Analyses

All subjects who received any dose of roxadustat were included in the safety analyses. Safety analyses were made by each roxadustat treatment arm and by pooled roxadustat treatment arm. All safety assessment data, including laboratory assessments (with special emphasis on Hb response and LFTs), vital signs, physical exams, ECGs, AEs, concomitant medications and therapies were summarized by treatment and time point of collection as appropriate. An AE data listing by subject, including verbatim term, preferred term, treatment, severity, and relationship to treatment, was analyzed. The number (%) of subjects experiencing treatment-emergent AEs was summarized by treatment using frequency counts.

Descriptive statistics were calculated for quantitative safety data and frequency counts were compiled for classification of qualitative safety data. Laboratory data was summarized for each time point that specimens were collected. Change-from-baseline values could be calculated for selected laboratory parameters (baseline refers to blood drawn prior to the first study treatment). Laboratory values outside of normal limits were identified in the subject data listings with flags for high and low values. Lab results obtained from the central laboratory were used for all safety analyses.

ECG results were classified using frequency counts for normal, clinically insignificant abnormalities, and clinically significant abnormalities by time point of collection. Descriptive statistics were calculated for QT intervals. Blood pressure, HR, and respiratory rate data were summarized descriptively by various time intervals both as absolute values and as changes from baseline. A summary table and/or listing presented all abnormal physical exam results throughout the study.

Determination of Sample Size

Sixty subjects were enrolled into this study, based on clinical judgment and experience from prior studies, to evaluate the corrective effect of roxadustat for treatment of anemia. Five treatment arms, each treatment arm consisting of 12 subjects, were chosen for evaluation of response to dosing regimens. The sample size was not determined by statistical power analysis.

Adverse Events Reported for ≥2 Subjects by System Organ Class and Preferred Term (MedDRA, Safety Population)

System Organ Class Preferred Term	**Arm A+E (N=24)**	**Arm B (N=12)**	**Arm C (N=12)**	**Arm D (N=12)**	**Overall (N=60)**
No. (%) of subjects with any TEAE	**16 (66.7)**	**6 (50.0)**	**3 (25.0)**	**5 (41.7)**	**30 (50.0)**
Blood and lymphatic system disorders	2 (8.3)	1 (8.3)	0	0	3 (5.0)
Thrombocytosis	2 (8.3)	0	0	0	2 (3.3)
Cardiac disorders	4 (16.7)	1 (8.3)	0	1 (8.3)	6 (10.0)
Gastrointestinal disorders	2 (8.3)	0	1 (8.3)	1 (8.3)	4 (6.7)
Infections and infestations	3 (12.5)	1 (8.3)	0	2 (16.7)	6 (10.0)
Device related infection	0	1 (8.3)	0	1 (8.3)	2 (3.3)
Injury, poisoning and procedural complications	3 (12.5)	1 (8.3)	2 (16.7)	3 (25.0)	9 (15.0)
Arteriovenous fistula thrombosis	1 (4.2)	1 (8.3)	0	0	2 (3.3)
Chemical peritonitis	0	0	0	2 (16.7)	2 (3.3)
Post-procedural haemorrhage	1 (4.2)	0	1 (8.3)	0	2 (3.3)
Procedural hypotension	2 (8.3)	0	0	0	2 (3.3)
Investigations	5 (20.8)	1 (8.3)	0	0	6 (10.0)
Transferrin saturation decreased	3 (12.5)	1 (8.3)	0	0	4 (6.7)
Serum ferritin decreased	1 (4.2)	1 (8.3)	0	0	2 (3.3)
Metabolism and nutrition disorders	1 (4.2)	0	0	1 (8.3)	2 (3.3)
Nervous system disorders	2 (8.3)	1 (8.3)	0	1 (8.3)	4 (6.7)
Headache	1 (4.2)	0	0	1 (8.3)	2 (3.3)
Respiratory, thoracic & mediastinal dis.	2 (8.3)	1 (8.3)	0	1 (8.3)	4 (6.7)
Epistaxis	1 (4.2)	1 (8.3)	0	0	2 (3.3)
Skin and subcutaneous tissue disorders	1 (4.2)	0	0	1 (8.3)	2 (3.3)
Rash	1 (4.2)	0	0	1 (8.3)	2 (3.3)
Vascular disorders	4 (16.7)	4 (33.3)	0	2 (16.7)	10 (16.7)
Hypertension	1 (4.2)	3 (25.0)	0	2 (16.7)	6 (10.0)
Phlebitis	2 (8.3)	1 (8.3)	0	0	3 (5.0)

Abbreviations: SOC = system organ class; TEAE = treatment emergent adverse events.

NOTE: A subject reporting more than one event in a category is counted only once in that SOC; however, a subject may have events in multiple SOCs causing the total TEAEs in the right hand column to be >2.

Serious Adverse Events Reported by System Organ Class and Preferred Term (MedDRA, Safety Population)

System Organ Class Preferred Term	Arm A+E (N=24)	Arm B (N=12)	Arm C (N=12)	Arm D (N=12)	Overall (N=60)
No. (%) of subjects with any TESAE	**3 (12.5)**	**1 (8.3)**	**0**	**3 (25.0)**	**7 (11.7)**
Cardiac Disorders	1 (4.2)	0	0	1 (8.3)	2 (3.3)
Cardiac failure acute	0	0	0	1 (8.3)	1 (1.7)
Cardiac failure chronic	1 (4.2)	0	0	0	1 (1.7)
Myocardial infarction	1 (4.2)	0	0	0	1 (1.7)
Gastrointestinal disorders	1 (4.2)	0	0	0	1 (1.7)
Gastrointestinal haemorrhage	1 (4.2)	0	0	0	1 (1.7)
Infections and infestations	1 (4.2)	1 (8.3)	0	0	2 (3.3)
Device related infection	0	1 (8.3)	0	0	1 (1.7)
Pyelonephritis chronic	1 (4.2)	0	0	0	1 (1.7)
Injury, poisoning and procedural complications	1 (4.2)	1 (8.3)	0	2 (16.7)	4 (6.7)
Arteriovenous fistula thrombosis	1 (4.2)	1 (8.3)	0	0	2 (3.3)
Chemical peritonitis	0	0	0	2 (16.7)	2 (3.3)

Abbreviations: N = number of subjects; SOC = system organ class; TESAE = treatment emergent serious adverse event.

Sites and Enrollment

Country	# of study sites	# of patients	% pts represented in study
Russia	13	56	93.3%
USA	2	2	3.3%
Hong Kong	1	2	3.3%

*Median [range] enrollment at Russian sites was 3 [1, 8] subjects

*SF-36 HRQOL Scores During Roxadustat Treatment**

SF-36		Baseline	Change from Baseline			
			8 Weeks		12 Weeks	
		mean (±SE)	mean (±SE)	p-value	mean (±SE)	p-value^
Norm-Based Domain Score	Physical Functioning	40.0 (±1.4)	3.3 (±1.0)	0.0017	3.9 (±1.0)	0.0002
	Role Physical	36.1 (±1.2)	3.6 (±1.0)	0.0011	3.9 (±1.1)	0.0007
	Vitality	47.3 (±1.5)	2.7 (±1.4)	0.0565	3.7 (±1.2)	0.0028
	Role Emotional	37.6 (±1.8)	3.5 (±1.6)	0.0285	3.3 (±1.4)	0.0228
Component Score	Physical Component Summary	41.1 (±1.1)	2.6 (±1.1)	0.0187	2.5 (±1.0)	0.0131
	Mental Component Summary	43.7 (±1.6)	1.5 (±1.3)	n.s.	2.2 (±1.1)	0.0453

*FACT-An HRQOL Scores During Roxadustat Treatment**

FACT-An	Baseline	Change from Baseline			
		8 Weeks		12 Weeks	
	mean (±SE)	mean (±SE)	p-value	mean (±SE)	p-value^
Physical Well-Being	19.3 (±0.8)	1.8 (±0.6)	0.0052	1.6 (±0.7)	0.0253
Emotional Well Being	16.4 (±0.6)	0.8 (±0.5)	0.0968	0.7 (±0.5)	n.s.
Anemia	52.4 (±2.1)	4.2 (±1.8)	0.0196	4.9 (±1.6)	0.0026
Total Score	123.3 (±4.4)	7.0 (±3.2)	0.0349	7.6 (±3.1)	0.0165

*Only those norm-based domain scores and component scores with statistical significant change from BL after 8 and/or 12 weeks are noted here. ^p-values are for change from BL.